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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/487,992	06/07/95	HALLENBECK	P 1136.0020001

EXAMINER

HM32/0413

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ART UNIT	PAPER NUMBER
NGUYEN, D	#19
1633	

DATE MAILED: 04/13/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on January 21, 1998

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-42 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-42 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

* U.S. GPO: 1998-404-498/40

Claims 1, 19, 29-39, and 40 have been amended, and claims 41 and 42 have been added by the response filed January 21, 1998. Regarding the amendment of claims 10 and 11 by the response by deleting --method-- at line 1 and inserting therefore "vector", the amendment is not entered because line 1 of claims 10 and 11 does not contain "method" as indicated in the response.

Information Disclosure Statement

Regarding the IDS filed October 30, 1997 (paper No. 16), the IDS has been placed in the application file, but the information has not been considered as to the merits because the references cited in said IDS and form 1449 are apparently missing. The references will be considered when the references are made of record.

Claims 1-42 are pending to which the following grounds of rejection remain or are applicable.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The second application (which is called a continuation-in-part) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht,* 168 USPQ 293 (CCPA 1971). While the parent application, 08/348,258, indicates at page 27 that a tissue-specific-conditional vector can be constructed using

a tissue specific promoter operably linked to a preferred adenovirus coding sequence necessary for viral replication, it is not apparent how the tissue-specific-conditional vector is constructed and produced so as to exhibit a tissue-specific conditional replication, *e.g.,* tissue specific replication only at target cells having appropriate transacting transcription factors, particularly given the reasons set forth in the following paragraphs. Note that the subject matter drawn to a promoter selected from group consisting of DF3, tyrosinase, CEA, surfactant, and ErbB2 (recited in claims 3 and 11) is not disclosed in the parent application 08/540,867. Thus, since the parent application 08/540,867 does not contain an enabling disclosure, the priority for the claimed tissue-specific conditional vectors, isolated cells containing the vectors, methods of producing and using the vectors can only be granted to the filing date of the instant application, June 7, 1995.

Claims 1-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject mater which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention drawn to a tissue-specific replication-conditional vector and method of using the tissue-specific replication-conditional vector for distributing a polynucleotide in a tissue *in vivo.*

The application indicates at page 7 that replication of the claimed vector is conditioned upon the presence of trans-acting transcriptional regulatory factors that permit transcription from a transcriptional regulatory sequence (heterologous), and that the regulatory sequence is specifically activated or derepressed in the target tissue so that the replication of the vector only

proceeds in that tissue. The application further indicates that in a preferred embodiments of the invention, the replication-conditional vector is a DNA tumor viral vector, *e.g.,* herpesevirus, papovavirus, papillomavirus, and hepatitis virus vector, and that in the most preferred embodiment, the vector is an adenovirus vector (p. 9). The application provides guidance as to the construction of the claimed vectors, but does not demonstrate with evidence that any of the disclosed vectors comprising a tissue specific regulatory sequence(s) is specifically activated for replication in a target tissue. The state of the art exemplified by Vile *et al.* (Molecular Medicine Today, Vol. 4, 2:84-92, 1998) indicates that development of effective transcriptionally targeted vectors remains unpredictable. For example, Vile *et al.* (p. 90, column 1) teach that "the relevant locus control regions/enhancer/silencer/promoter sequences that control expression can be distributed over many kbp and within chromatin domains that are difficult to reproduce within the context of the vector systems, and that "the combinations of these elements in certain configurations of these elements in certain configurations might be successful in the context of one vector (such as plasmid DNA), but their specificity might be altered or lost in a different context (such as retrovirus or adenovirus). Russel (European Journal of Cancer, Vol. 30A, 8:1165-1171, August 1994) states that "cell-specific utilisation of the albumin (liver specific) and immunoglobulin (B-cell specific) promoters has been demonstrated within non-replicating adenovirus genomes but cell specificity was partially lost after replication of the viral DNA", and that the stoichiometry and kinetic of gene regulation by cellular transcription factors must be known for engineering the promoters of replicating vectors for tissue-specific, transformation-

dependent expression (p. 1168, column 2). Thus, it is not apparent how one skilled in the art determines as to which of the tissue-specific replication-conditional vectors recited in claim 1 is tissue specific for replication without undue experimentation on the basis of applicant's disclosure, particularly given the doubts expressed in the art of record. With regard to claims directed to tissue-specific replication-conditional adenoviral vectors (which is a preferred species of the claimed invention), the adenoviral genes, E1b, E2, E1A, and E4 (all essential for replication of adenovirus vectors) encode proteins whose functions are dissimilar with each other. Each of these genes or regions require a certain level of expression to support adenoviral replication. Note also the application indicates at page 6 that expression levels of adenoviral genes essential for replication, *e.g.*, E1 and E4, must be carefully regulated in order to averse toxicity effect of the adenoviral genes upon the cells or tissues transformed with adenovirus vectors. Since it is known in the art that tissue-specific cellular promoters activate constitutive expression of a transgene in a target tissue, it is not apparent how the expression levels of E4 gene, for example, are regulated from the claimed adenoviral vectors in order to avoid the toxicity to transformed cells (due to uncontrollable expression of E4 genes) prior to the replication and growth of the replication-conditional adenovirus vectors. There is no discussion in the specification of expression levels necessary to achieve appropriate expression for specific replication in a target tissue or cells *in vitro* and/or *in vivo*. Note that the application indicates at page 9 that the most preferred vector of the claimed invention is an adenovirus vector.

With regard to claims 3 and 11 drawn to the use of specific heterologous tissue specific promoters in the construction of the claimed vectors, an artisan, attempting to make and use the claimed vectors, would first look to the specification for guidance as to the availability of heterologous tissue-specific transcriptional regulatory sequences recited claims 3 and 11. However, the specification is not enabling for the claimed vectors containing the promoters selected from group consisting of tyrosinase, CEA, surfactant, and ErbB2 (recited in claims 3 and 11). The specification indicates that the promoters can be cloned and sequenced by PCR technology using the primers depicted in Table 1, however, it is not apparent how one skilled in the art clones, sequences, and employs the DNA sequence(s) encoding the functionally active promoters in the conditional replication vectors with a reasonable expectation of success and without undue experimentation, particularly since it is not apparent as to what is the length and the exact location of the DNA sequence(s) encoding the promoters, and as to whether there are more than one locus control regions and/or enhancers and/or silencers and/or promoter sequences involved in the make-up of the DNA sequences encoding the functionally active promoters recited in the claims. Note that Vile *et al.* (p. 90, column 1) teach that "the relevant locus control regions/enhancer/silencer/promoter sequences that control expression can be distributed over many kbp and within chromatin domains that are difficult to reproduce within the context of the vector systems".

Thus, one skilled in the art cannot identify, without undue experimentation, a tissue in which all of the replication-conditional vectors recited in claim 1 are specifically replicated *in vitro*

and/or *in vivo* by means of the transcriptional regulatory sequence contained in the vectors, particularly given the reasons set forth in the preceding paragraphs.

As to claims 9-18 drawn to methods of distributing a polynucleotide in a tissue *in vivo* using the claimed vectors, the application on page 12 indicates that "the object of the distribution is to deliver the vector, gene product or the effects of the gene product (as by a bystander effect, for example) to substantially number of cells of the target tissue, so as to treat substantially the entire target tissue". Thus, the claims encompass gene-targeted therapy in any subject including a human and implanted cells containing the claimed vector for generating a therapeutic effect. Major considerations for any gene transfer or gene therapy protocol involve issues such as amount of DNA constructs to be administered, what amount is considered to be therapeutically effective for all of the claimed nucleic acid molecules, the route and time course of administration, the sites of administration, successful uptake of the claimed DNAs at the target site, expression of the DNAs at the target site in amounts of effecting the claimed methods (Crystal, Science, Vol. 270:404-409, 1995; Coghlan, New Scientists, Vol. 148:14-15, 1995). Gunzburg *et al.* (Molecular Medicine Today, pp. 410-417, 1995) state that "clearly, there are many problems to be overcome before gene therapy becomes a widely used treatment , and it will probably only ever complement rather than replace existing therapies" (p. 417). Gunzburg *et al.* also state that "the efficiency of gene delivery is perhaps the most limiting technical problem; this will require extensive modifications to existing vector systems or even the construction and development of new gene delivery systems (p. 416, column 2, last paragraph). Regarding the state of the art of

gene therapy for human cancer, Mastrangelo *et al.* (Seminars in Oncology, Vol. 23, No. 1:4-21, 1996) states that "to date the major successes with gene therapy for cancer have been limited to *in vitro* systems where tumor cells with well defined genetic defects are easily targeted" (p. 13, column 2). Mastrangelo *et al.* further state that "Critical to the success of gene therapy is the efficient transfer (transfixing) of a functioning gene to the target cell" and that "this has prevented a major stumbling block, particularly for *in vivo* gene transfer" (p. 10, column 1). Regarding *ex vivo* gene therapy, Mastrangelo *et al.* disclose that adoptive immunotherapy (*e.g.* infusion of cytotoxic cells such as genetically modified macrophage cells), which has been known to be effective *in vitro*, is not necessarily effective *in vivo* (pp. 18-19). Ledley (Human Gene Therapy 6:1129-1144, 1995) states that "every somatic target exhibits distinct properties, and the rate-limiting steps in gene delivery and expression may be expected to be different" and that "it is unlikely that any one method for gene transfer will prove to be effective in every organ" (p. 1139). While the specification provides a list of such promoters, there is no guidance as to those specific promoters which could be taken and used in the claimed vectors. It is a necessary element of the claimed invention that the tissue specific promoters express the gene necessary for replication sufficient to foster replication specifically in a disease site, with the result of *in vivo* gene expression so as to have a therapeutic effect. Thus, a showing of promoters and promoters regions that provide such specificity and such sufficiency is necessary for the implementation of the invention. A listing of promoters known in the art at the time of filing may provide a germ of an idea, but that is not sufficient guidance to apply the promoter to

vector and obtain specific vector replications and sufficient transgene expression at a target tissue *in vivo* so as to generate a therapeutic effect. Thus, without guidance from the specification the artisan would have been required practice undue experimentation to construct and use the claimed vectors.

In view of the lack of guidance regarding the administration parameters, lack of convincing data or working examples, breadth of the claims, state of the art and the unpredictability of the art, as set forth by the evidence presented above, undue experimentation would be required by one of ordinary skill to practice the invention as claimed.

The comments regarding the 112, first paragraph issues in the response of January 21, 1998 have been considered (pp. 7-13) but they are not persuasive for the reasons indicated in this Office Action.

In response to applicant's assertion that the present rejection of claims 9-18 has been based entirely on consideration of only one of the *Forman* factors: the predictability factor, particularly since the noted comments by Crystal, Coghlan, Gunzburg, Mastrangelo, Ledley, Dilon, Pennisi, and Orkin and Motulsky simply indicate that there was no clinical evidence, as of the date of filing of the present application, that genetic treatment has produced therapeutic benefits (p. 8 bridging p. 9), the comments are not persuasive because the instant and prior Office actions did not state a requirement for clinical data. The above argument by applicant does not factually establish a correlation between the factual data obtained from applicants disclosure to the enablement of the claimed invention, given the doubts expressed by the art of record, as set forth

in the previous and in this Office action. As stated in the previous Office actions, the methods recited in claims 9-18 are not enabled as the specification only discloses the method for distributing a polynucleotide sequence in a tissue *in vivo* within the context of gene therapy, *e.g.*, cancer therapy. In view of the lack of any established nexus between the guidance showing constructions of the claimed conditional-replication vectors to a therapeutic effect using the claimed methods, one must evaluate the evidence presented and determine whether applicant has demonstrated such correlation or a reasonable likelihood of such. In the instant case, the guidance presented in the as-filed specification support a conclusion of unpredictability and lack of reproducibility. This conclusion coupled with state of the art is consistent with a finding of lack of enablement for the practice of what is claimed. Applicants arguments fail to address these art recognized limitations in the transient expression of a gene product *in vivo* as applicable all *in vivo* gene expressions using any therapeutic gene to have a therapeutic effect in all treated subjects. While the specification provides a list of such promoters, there is no guidance as to those specific promoters which could be taken and used in the claimed vectors. It is necessary from the claimed invention that the tissue specific promoters express the gene necessary for replication sufficiently to foster replication specifically in a disease site, with the result of *in vivo* gene expression so as to have a therapeutic effect. Thus, a showing of promoters and promoter regions that provide such specificity and such sufficiency is necessary for the implementation of the invention. A listing of promoters known in the art at the time of filing may provide a germ of an idea, but that is not sufficient guidance to apply the promoter to vector and obtain specific

vector replications and sufficient transgene expression at a target tissue *in vivo* so as to generate a therapeutic effect. Thus, based upon the evidence in the record, which demonstrates that there is a reasonable basis for questioning the assertions regarding the enablement of the claimed invention, the present claims are properly rejected under 35 U.S.C. 112, first paragraph, and discussions of *Ex parte Forman, In re Wands* as to "undue experimentation" are not persuasive.

In response to applicant's assertion that "it is well known that *in vitro* studies are accepted by those with ordinary skill in the art of gene therapy and pharmacology as being predictive of success *in vivo*", and that *Cross v. Iizuka* and *In re Brana* support the assertion (p. 9), the comments are nor persuasive. While *Cross v. Iizuka* is directed to enablement issues under 112, first paragraph regarding "how to use" imidazole derivative compounds which exhibit a pharmacological activity, the claimed invention of this application is directed to methods for distributing a polynucleotide at a target tissue *in vivo* so as to have a therapeutic effect, *e.g,* treating any pathophysiological state in a human. Thus, it is not apparent how *Cross v. Iizuka* is reasonably correlated to the claimed invention, nor is it apparent the present application claims are directed to a prosthetic device for which applicant relies upon *In re Brana.* Note that the claimed tissue-specific-conditional vectors are not enabled for *in vitro* and/or *in vivo* use, as stated in this Office action.

In response to applicant's assertion that since there are other uses of the methods recited in claims 9-18 which are unrelated to therapy, including but not limited to the production of a cell line that produces large amounts of the present vectors, it is improper for the Examiner to reject

the claims based on the possibility of allegedly inoperable embodiments (p. 10), the comments are not persuasive. A method for producing a cell line that produces large amounts of the present vectors in culture (see pp. 8 bridging p. 9 of the specification) is not the same as a method for distributing a polynucleotide in a target tissue *in vivo*. Furthermore, since the methods as claimed encompass *in vivo* gene transfer methods so as to generate a therapeutic effect in all target cells of all mammals, it is not apparent how one skilled in the art determines which of the mammals are affected by the claimed method, particularly given the Crystal reference indicating that "Humans are not simply large mice" (p. 409).

It is noted that the response filed April 17, 1997 indicates that the working examples describing construction the specific plasmid vectors by incorporation by reference from U.S. copending application are working examples only, and are not essential for practicing the claimed invention, particularly since the Examiner has not provided specific evidence or scientific reasons to support the position that vectors described in the working examples are essential for practicing the claimed invention. However, upon a further consideration, applicant's comments are not persuasive. The presently pending claims are drawn to tissue-specific-conditional vectors, cells which produce the vectors, and methods of using the vectors. Thus, the claims are generic and do not exclude the vectors described in the working examples. An artisan, attempting to make and use the claimed tissue-specific-conditional vectors, would first look to the specification for guidance as to the construction and production of such vectors. Since the manufacture of plasmids PAVS21.TK1 and SE280-E1, which are fundamental to the construction of the tissue-

specific adenovirus vectors (which is one of the claimed species recited in the claims) is described in the working examples only by the improper incorporation of references to other, pending, patent applications which are not identified by any serial number. The attempt to incorporate essential material into this application by reference to a copending US application is improper because only allowed U.S. applications and U.S. Patents can be incorporated by reference. While applicants indicated in the response filed April 17, 1997 that given the general principles disclosed in the specification, the claimed vector could have been built from any virus in which the genes essential for replication had bee characterized, with any of the various known promoters (p. 3), it is not apparent how such vectors exhibit the tissue-specific-conditional replication, particularly in view of the reasons set forth in the preceding paragraphs.

In response to applicant's assertion that claims 9-18 encompassing the potential use of, or methods involving, *in vitro* and *in vivo* applications of the claimed vectors are fully enabled by the present and original specification in view of citations of *Guidlines for Examination of Applications for Compliance with the Utility Requirement,* and *In re Brana,* the comments are not persuasive because the statutory ground of rejection is not for utility under 35 U.S.C. 101 but for lack of enablement under 35 U.S.C. 112 first paragraph. A finding that applicant's assertions are credible does not necessitate a finding that, based upon the as-filed specification, one skilled in the art would have been able to have practiced what is claimed. Furthermore, the issue at hand is not usefulness *per se*, but rather whether one skilled in the art would have been able to have practiced what is claimed based upon the as-filed specification. The page 11 discussion regarding

the FDA and requirement of clinical data is noted, however, the rejection is not based upon FDA requirement nor its rules. Thus, commentary regarding same is not persuasive nor are the present application claims directed to a prosthetic device for which applicant relies upon In re Brana. However, it is noted that there is no question of utility *per se*, raised either in the previous Office action or this Office action. The previously and above stated rejections are indicative of unpredictability which leads to doubt of the objective statements in the present application, thus citations of Utility Guidelines and *In re Brana* are not persuasive of applicant's position.

In response to applicant's assertion that since the art is replete with various examples of successful transfection of nucleic acid molecules *in vivo,* it would be clear to the skilled artisan that the same types of transfections may now be done using the vectors, compositions and methods of the present invention to increase gene expression in target cells and tissues *in vivo* (p. 11 bridging p. 12), the comments are not persuasive. The present application does not present expectation of success (of that therapeutic effect) in that regard as to the expression of all transgenes to have a therapeutic effect in all animals, particularly since applicants arguments do not factually establish such correlation on the basis of applicants disclosure. In addition, when considering *in vivo* expression of a gene product at a target tissue to have a therapeutic effect, simple expression at a cell *in vivo* is not sufficient. Furthermore, it is known in the art that while some progress has been made toward human gene therapy, only a handful of clinical trials and very limited anecdotal results has been reported to date. Thus, the unpredictability of a particular

art area alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of a claim.

The following is a quotation of the second paragraph of 35 U.S.C. 112, second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the application regards as his invention.

Claims 9-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10 and 11 are vague and indefinite since the claims refer to the vector of claim 9; however, claim 9 is directed to a method claim. For the purpose of compact prosecution, it is assumed that claims 9 and 10 refer to the method of claim 9.

Claims 9-16 are indefinite because it is not apparent as to what is the stated effect of the distribution of a polynucleotide *in vivo* in accomplishing a beneficial effect.

Claim 17 is indefinite because it is not apparent as to what is the stated effect of *in vivo* gene expression of a heterologous gene in accomplishing a beneficial effect.

Claim 18 is indefinite because it is not apparent as to what are the metes and bounds of the anti-tumor activity of "said heterologous gene product". Does the anti-tumor activity cure, prevent, stimulate, or inhbit the growth of a tumor in all target tissues *in vivo*?

Claims 1-5, 8-14, 17-24, 27-35, and 38-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza *et al.* (US Pat No. 5,728,379).

Martuza *et al.* disclose a method for killing tumor cells *in vivo* comprising administration of tissue-specific-replication competent herpes simplex virus vectors to tumor cells. The tissue-specific-replication competent herpes simplex virus vectors contain a tissue-specific or cell-specific transcriptional regulatory sequence that is operatively linked to an essential herpes simplex virus gene, wherein said transcription regulatory sequence effects expression of said gene in a specific tissue or cell, such that said virus replicates only in said tissue or cell. Claims 1-13 are directed to the method and the replication competent herpes simplex virus vectors. The claimed invention of the '379 patent is fully disclosed and enabled by the specification of the parent U.S. Pat No. 5,585,096. In the '096 patent, columns 11 and 12 disclosed the tissue-specific-replication competent herpes simplex virus vectors and methods of using the herpes simplex virus vectors to express a heterologous gene for specific killing of tumor cells. Columns 15 and 16 provide a guidance as to how to construct the tissue-specific-replication competent herpes simplex virus vectors. Examples 2-5 provide a detailed description as to how to use the replication-competent viral vectors in *in vivo* extracranial and *in vivo* intracranial tumor killing models. Given that tissue-specific promoters selected from group consisting of α-fetoprotein, DF3, tyrosinase, and ErbB2 are known in the art prior to the effective filing date of the as-file application (see Tables 1 and 2 of the '379 patent), it would have been obvious for one of ordinary skill in the art to have constructed and employed the tissue-specific-replication

competent herpes simplex virus vectors of Martuza *et al.* using a known tissue-specific promoter operably linked to a viral gene necessary for herpes simplex virus replication for expressing a heterologous gene, *e.g.*, cytokines, in a tumor cell-specific fashion in order to target an immune response that kills the tumor cells. One of ordinary skill in the art would have a reasonable expectation of success in constructing and employing the tissue-specific-replication competent herpes simplex virus vectors of Martuza *et al.* for distributing and expressing a polynucleotide at a tissue *in vivo,* particularly given that claims 1-13 of the '379 patent recite the same.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Claims 1-5, 8-14, 17-24, 27-35, and 38-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza *et al.* (US Pat No. 5,585,096).

Martuza *et al.* disclose and a method for killing tumor cells *in vivo* comprising administration of tissue-specific-replication competent herpes simplex virus vectors to tumor cells. The tissue-specific-replication competent herpes simplex virus vectors contain a tissue-specific or cell-specific transcriptional regulatory sequence that is operatively linked to an essential herpes simplex virus gene, wherein said transcription regulatory sequence effects expression of said gene in a specific tissue or cell, such that said virus replicates only in said tissue or cell. Columns 11 and 12 disclosed the tissue-specific-replication competent herpes simplex virus vectors and methods of using the herpes simplex virus vectors to express a heterologous gene for specific

killing of tumor cells. Columns 15 and 16 provide a guidance as to how to construct the tissue-specific-replication competent herpes simplex virus vectors. Examples 2-5 provide a detailed description as to how to use the replication-competent viral vectors in *in vivo* extracranial and *in vivo* intracranial tumor killing models. Given that tissue-specific promoters selected from group consisting of α-fetoprotein, DF3, tyrosinase, and ErbB2 are known in the art prior to the effective filing date of the as-file application (see Tables 1 and 2 of the '379 patent), it would have been obvious for one of ordinary skill in the art to have constructed and employed the tissue-specific-replication competent herpes simplex virus vectors of Martuza *et al.* using a known tissue-specific promoter operably linked to a viral gene necessary for herpes simplex virus replication for expressing a heterologous gene, *e.g.,* cytokines, in a tumor cell-specific fashion in order to target an immune response that kills the tumor cells. One of ordinary skill in the art would have a reasonable expectation of success in constructing and employing the tissue-specific-replication competent herpes simplex virus vectors of Martuza *et al.* for distributing and expressing a polynucleotide at a tissue *in vivo,* particularly given that columns 15, 16, and Examples 2-5 provide a detailed description as to how to construct and employ such vectors for killing tumor cells in a specific fashion.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Claims 1-8, and 19-42 are rejected under 35 U.S.C. 102(b) as being anticipated by, or in the alternative, under 35 U.S.C. 103 as being unpatentable over Babiss *et al.* (J. Mol. Biol. 193, 643-650, 1987).

Babiss *et al.* teach a replication competent adenovirus where the promoter for albumin gene, a liver specific promoter, regulates the expression of E1a and E1b in liver cells (p. 645, col. 2, lines 1-19). Babiss *et al.* indicate that the vector can be used in assays to determine the effect of replication on the expression of endogenous genes (p. 649, col. 1, lines 4-8). Fig. 2 depicts transcription pattern in HepG2 cells after infection by alb194 virus. Column 2 at page 645 states that "injection with the abl454 virus, which includes the E1A enhancer upstream from the albumin promoter and results in a five fold increase in transcription rate from the exogenous albumin promoter on the virus". To the extent that the reference is ambiguous regarding the use of a tissue specific promoter selected from group consisting of α-fetoprotein, CEA, DF3, tyrosinase, and ErbB2, it would have been obvious for one of ordinary skill in the art at the time of the invention to make the adenoviral vector of Babiss *et al.* by employing any of the known tissue-specific promoters such as α-fetoprotein, CEA, DF3, tyrosinase, and ErbB2, particularly since Tables 1 and 2 of the '379 patent indicate that such promoters are known and available at the time the invention was made. Thus, absent evidence to the contrary, and in the alternative, the adenoviral vector of Babiss *et al.* has all of the properties cited in the claims.

Double Patenting

1. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum,* 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman,* 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. **Claims 1-42** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable claims 1-40 of US application No. 08/849,117. Although the conflicting claims are not identical, they are not patentably distinct from each other because both set of claims are directed to drawn to a tissue-specific replication-conditional vector, isolated cells containing the tissue-specific replication-conditional vector, method of producing the vectors, and methods of using the tissue-specific replication-conditional vector for distributing a polynucleotide in a tissue *in vivo.*

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No claims are allowed.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 1600, Art Unit 1633.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Jacqueline Stone*, may be reached at **(703) 305-3153**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 304-0196**.

Dave Nguyen

April 8, 1998

Christopher S. F. Low

CHRISTOPHER S. F. LOW
PRIMARY EXAMINER
GROUP 1800

Jasemine C. Chambers

JASEMINE C. C...
SUPERVISORY PA...
GROUP ...